A STUDY OF CLINICAL BIOCHEMICAL, SONOLOGICAL PROFILE OF HEPATIC STATUS IN TYPE 2 DIABETES MELLITUS IN TERTIARY CARE SETTING

Dissertation submitted in partial fulfillment of regulation for the award of

M.D. Degree in General Medicine (Branch I)

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Dr. M.G.R. Medical University
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Certificate

Certified that this is the bonafide dissertation done by ***DR. MOHAMED SHIHAB.P*** *and submitted in partial fulfillment of the requirements for the Degree of M.D., General Medicine, Branch I of The Tamilnadu Dr. M.G.R. Medical University, Chennai.*

Date : Professor and Chief of Medical Unit IV

Date : Professor & Head
Department of Medicine

Date : Dean
Coimbatore Medical College
Coimbatore - 641 010

DECLARATION

I solemnly declare that the dissertation titled **"A STUDY OF CLINICAL,BIOCHEMICAL,SONOLOGICAL PROFILE OF HEPATIC STATU IN TYPE 2 DIABETES MELLITUS IN TERTIARY CARE SETTING"** was done by me from January 2008 to August 2009 under the guidance and supervision of Professor **Dr.NEDUMARAN.MD. DM**

This dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

Dr.MOHAMED SHIHAB .P

Place: Coimbatore

Date: 01.12.2009

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CONTENTS

INTRODUCTION

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The prevalence of diabetes is increasing world over and is expected to affect 57 million adults in india by 2025.

Apart from kidney, eye, heart and blood vessels, liver is also indirectly related with diabetes mellitus. Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes. This includes abnomal liver enzymes, non alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure. In addition, there is an unexplained association of diabetes with hepatitisC.

Finally, the prevalence of diabetes in cirrhosis is 12.3–57% . Thus, patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes

NAFLD

Ludwig introduced the term Nonalcoholic steatohepatitis (NASH) to describe a form of liver disease that is histologically indistinguishable from alcoholic hepatitis but occurs in people who do not consume excess ethanol.[1] There is renewed interest in Non alcoholic fatty liver (NAFL) recently because of its

increased prevalence in diabetes. It has been shown to be a predisposing factor for insulin resistance and hyperinsulinemia, a major cause of cryptogenic cirrhosis and may even lead to hepatocellular carcinoma.[2,3,4]

Nearly 70-80% of the diabetic subjects have been reported to have hepatic fat accumulation, referred to as NAFLD.[5] There are not enough studies done on the hepatic status of diabetic patients in our country. Hence this study aims to describe the hepatic profile of type 2 diabetic patients.

NAFLD represents a spectrum of diseases from simple fatty liver (steatosis), to steatosis with inflammation, necrosis, and possible cirrhosis, that occurs in people who drink little or no alcohol.

NAFLD affects more women than men and can be found in all age groups diabetes, by most estimates, is now the most common cause of liver disease in the U.S. Cryptogenic cirrhosis, of which diabetes is, by far, the most common cause, has become the third leading indication for liver transplantation

.The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. So Insulin resistance is the main culprit in the pathogenisis of fatty liver

. The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance, however, is not fully understood.

Despite down-regulation of the insulin receptor substrate-2-mediated insulin signaling pathway in insulin-resistant states, the up-regulation of SREBP-1c(sterol regulatory element protein 1 c) and subsequent simulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver. This also increases VLDL assembly and deposition in liver.

. The insulin-resistant state is also characterized by an increase in pro inflammatory cytokines such as tumor necrosis factor- (TNF-), which may also contribute to hepatocellular injury.

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AIM OF STUDY

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This study aims to describe clinical, biochemical, sonological profile of hepatic status in type 2 diabetes mellitus in tertiary care setting in relation with non alcoholic fatty liver disease (NAFLD)

REVIEW OF LITERATURE

RIVEW OF LITERATURE

The Role of the Liver in Glucose Homeostasis

An appreciation of the role of the liver in the regulation of carbohydrate homeostasis is essential to understanding the many physical and biochemical alterations that occur in the liver in the presence of diabetes and to understanding how liver disease may affect glucose metabolism. The liver uses glucose as a fuel and also has the ability to store it as glycogen and synthesize it from noncarbohydrate precursors (gluconeogenesis). Mann and Magath demonstrated that a total hepatectomy in a dog results in death within a few hours from hypoglycemic shock , underscoring the important role the liver plays in maintaining normoglycemia.

Glucose absorbed from the intestinal tract is transported via the portal vein to the liver. Although the absolute fate of this glucose is still controversial, some authors suggest that most of the absorbed glucose is retained by the liver so that the rise in peripheral glucose concentration reflects only a minor component of postprandial absorbed glucose. Therefore, it is possible that the liver plays a more significant role than does peripheral tissue in the regulation of systemic blood glucose levels following a meal, suggesting that most absorbed glucose is not

taken up by the liver but is rather metabolized via glycolysis in the peripheral tissues.

Many cells in the body, including fat, liver, and muscle cells, have specific cell membrane insulin receptors, and insulin facilitates the uptake and utilization of glucose by these cells. Glucose rapidly equilibrates between the liver cytosol and the extracellular fluid. Transport into certain cells, such as resting muscle, is tightly regulated by insulin, whereas uptake into the nervous system is not insulin-dependent. Glucose can be used as a fuel or stored in a macromolecular form as polymers: starch in plants and glycogen in animals. Glycogen storage is promoted by insulin, but the capacity within tissues is physically limited because it is a bulky molecule.

Glucose can be used as a fuel or stored in a macromolecular form as polymers: starch in plants and glycogen in animals. Glycogen storage is promoted by insulin, but the capacity within tissues is physically limited because it is a bulky molecule. Insulin is metabolized by insulinase in the liver, kidney, and placenta. About 50% of insulin secreted by the pancreas is removed by first-pass extraction in the liver. Insulin promotes glycogen synthesis (glycogenesis) in the liver and inhibits its breakdown (glycogenolysis). It promotes protein, cholesterol, and triglyceride synthesis and stimulates formation of very-low-

density lipoprotein cholesterol. It also inhibits hepatic gluconeogenesis, stimulates glycolysis, and inhibits ketogenesis. The liver is the primary target organ for glucagon action, where it promotes glycogenolysis, gluconeogenesis, and ketogenesis . The formation of glucose from lactate and various noncarbohydrate precursors is known as gluconeogenesis and occurs mainly in the liver and kidneys.

The liver, kidney, intestine, and platelets contain the enzyme glucose-6-phosphatase, which produces glucose from glucose-6-phosphate and is the final step in the production of glucose via gluconeogenesis. This enzyme is absent in other tissues. Glucose that is metabolized peripherally may therefore be converted back to glucose or to hepatic glycogen via gluconeogenesis with lactate as the primary substrate, this is known as Cori cycle.

In type 2 diabetes, excessive hepatic glucose output contributes to the fasting hyperglycemia. Increased gluconeogenesis is the predominant mechanism responsible for this increased glucose output, while glycogenolysis has not been shown to be increased in patients with type 2 diabetes . Hyperglucagonemia has been shown to augment increased rates of hepatic glucose output, probably through enhanced gluconeogenesis

Key signaling pathways involved in glucose homeostasis in the liver

Binding to the glucagon receptor on hepatocytes activates the serine/threonine kinase , this kinase causing phosphorylation and activation of glycogen phosphorylase kinase (GPK) and subsequently glycogen phosphorylase (GP), thus activating glycogenolysis. An increase in intracellular cyclic AMP also induces gluconeogenesis enzymes (phosphoenolpyruvate carboxykinase [PEPCK] and glucose-6-phosphatase [G6Pase]) *via* induction of peroxisome proliferator activated receptor-γ co activator 1α (PGC-1α) It should be emphasized, however, that under fasting conditions (potentially hypoglycemic conditions, in particular), non-hormonal mechanisms (principally hepatic auto regulation by glucose itself) are capable of supplying a significant proportion (up to 50%) of the body's glucose requirements *via* enhancement of both glycogenolysis, glucose cycling and eventually gluconeogenesis) .

The pathways involved in insulin signalling in the liver are highly complex involving hundreds of signaling molecules[38,39] ,and thus a myriad of potential points for modulation and interaction with other pathways, such as those involved in glucose auto regulation. Insulin signaling processes also appear to differ in different tissues.

The first key component in the signaling process is the insulin receptor itself and the associated intracellular insulin receptor substrate (IRS) proteins[39] . The IRS-2 subtype appears to play a more prominent role in the liver, whereas the IRS-1 subtype may be more important in skeletal muscle[40] and these two proteins have different capacities to interact with downstream signaling elements[41]. Within the liver, IRS-1 has been more closely linked with glucose homeostasis, whereas IRS-2 may be more closely linked with lipid metabolism[42] although surprisingly, liver-specific knockout of IRS 2 in mice does not appear to impair hepatic glucose and lipid metabolism[43]

The second key component involves the activation of the phosphatidyl inositol 3-kinase (PI3K) pathway, which appears to be crucial for insulin's metabolic actions *in vivo* in the liver.[44] After PI3K activation, the specific regulation of glucose and lipid homeostasis by insulin in the liver diverges PI3K dependentactivation of Akt (also known as protein kinase B [PKB]) appears to regulate factors involved in gluconeogenesis, whereas PI3K-dependent activation of atypical forms of protein kinase C appears to regulate factors involved in lipogenesis . For instance, pathway downstream of Akt leads to inactivation of phosphorylase, activation of glycogen synthase, and stimulation of glycogen synthesis, thus counteracting the effects of glucagon

In addition to acute effects on metabolic processes, insulin can also induce changes in genetranscription in the liver down-stream of the PI3K pathway[45,46]. Insulin can influence the expression of over 150 genes — this occurs *via* key transcription factors, such as FOXO1 that inhibits expression of PEPCK and G6Pase and inhibits gluconeogenesis), sterol-response element binding proteins (SREBPs) that primarily regulate genes involved in lipid synthesis), and specificity protein 1 (Sp1) that regulates genes for insulin receptors and leptin).

Hence the liver may play a much more important role than the peripheral tissues in regulating the normal blood glucose. Liver also removes about 50% of the insulin secreted by the pancreas during its first pass through the liver.

NON ALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) includes a wide spectrum of liver injury ranging from simple steatosis to steatohepatitis, fibrosis, and cirrhosis. Whereas simple steatosis has a benign clinical course, steatohepatitis is a recognized cause of progressive liver fibrosis and can develop into cirrhosis. NAFLD and nonalcoholic steatohepatitis (NASH) are the two most common chronic liver diseases in United States general population with a prevalence of 20% and 3%, respectively. Hepatic steatosis is frequently associated with obesity,

type 2 diabetes, and hyperlipidemia with insulin resistance as a key pathogenic factor.

PREVALENCE AND NATURAL HISTORY

Little is known about the prevalence or natural history of NASH. Biopsy evidence is available primarily from the relatively few symptomatic patients. Sequential biopsies in patients with NASH are particularly uncommon. If biopsy specimens had been obtained, it is often difficult to determine from the morphological descriptions whether fatty changes or steatohepatitis had been present. Furthermore, NASH may be missed because by the time biopsies are done, most fatty changes may have disappeared so that the hepatitis or cirrhosis is considered cryptogenic. Nevertheless, some rough estimates can be made. For example, in a study of 4613 male Japanese company employees, 534 were moderately obese and almost half had hepatic steatosis as judged by computed tomography. Twenty-four per cent of these obese patients had abnormal alanine aminotransferase (ALT) activities. A subsequent study revealed ultrasonographic evidence of fatty livers in 14% of 2574 patients from Okinawa. Fatty change was most common in persons between 40 and 49 years of age. Obesity was the strongest associated factor in both sexes; however, in males alcohol also was a

strongly associated factor[48]. In an autopsy study NASH was found in 18.5% of markedly obese patients and in 2.7% of lean patients.

As stated, most cases of NASH have been described in women with or without diabetes, but recent studies[47] suggest that the condition is also common in men and that obesity, hyper lipidaemia and glycemia are not prerequisites. Non-alcoholic fatty liver without appreciable inflammation or fibrosis appears to be the most common manifestation of NASH, although by strict criteria it is not a hepatitis. Thus, in a recent study of 14 patients with obesity and diabetes-related NASH and a median follow-up of 11 years (range 7-16 years), none developed evidence of progressive liver diseases[48] . However, transition from the uncomplicated non-progressive fatty liver to slowly progressive NASH may be difficult to discern because biopsy samples are often reviewed without the use of the tell-tale connective tissue stains and because sampling variations exist, as in most other liver diseases.

The development from NASH to steatohepatitic cirrhosis was clearly documented in a study of [47] patients who had been observed for 1.5-21.5 years (median 4.5 years); two patients developed cirrhosis that, in one instance, was complicated by hepatocellular carcinoma (HCC). The degree of obesity, hyper lipidaemia and hyperglycaemia did not correlate with the severity of the histological changes. Although some studies show progression in NASH to be

rare and, if it occurs, very slow, the Mayo Clinic experiences with NASH suggest a less favorable scenario.

NAFLD and associated conditions

NAFLD is associated with various conditions, which may be considered while diagnosing it. It is mainly associated with:

Obesity (69 - 100%)

Diabetes mellitus (36 - 75%)

Hyperlipidaemia (20 - 81%)

These conditions are associated with insulin resistance and metabolic syndrome, which is frequently observed with NAFLD.

Obesity: More than 70% of patients with NASH are obese. Body weight ranging from 10 - 40% higher than ideal is associated with 4 - 6 fold higher incidence of NAFLD. There is direct correlation between the severity of obesity and severity of NAFLD.

Diabetes: Upto 75% patients with NASH have diabetes mellitus. Obese, middle-aged females with DM are more likely to have fatty liver changes on ultrasonography

Hyperlipidaemia: 20 - 80% of patients with NASH have hyperlipidaemia in the form of high blood cholesterol level and/or high triglyceride levels.

Other associated conditions:

Total parenteral nutrition for prolonged periods.

severe insulin resistance.

Significant and rapid weight loss in obese subjects.

Familial lipid disorders, e.g., aβ-lipoproteinaemia, hypo β- lipoproteinaemia.

Limb lipodystrophy.

Weber-Christian disease.

Drugs: corticosteroids, methotrexate, tamoxifen,

PROGRESSION OF DISEASE

The progression from steatosis to steatohepatitis to cirrhosis and, in some patients, to hepatocellular carcinoma over a period of many years is well established . The prognosis worsens with each stage of disease. Why some patients progress while most do not is not known. The only reliable way, to date, of determining this progression is liver biopsy, which may have significant economic implications (good or bad) for the management of patients with type 2 diabetes.

It is tempting and perhaps deceptively intuitive to think that, in some people, simple fatty liver progresses to steatohepatitis and then to fibrosis and cirrhosis. However, an equally plausible alternate hypothesis is that individuals prone to develop necro inflammatory injury do so as the fat accumulates.

In fact, the limited long-term follow-up studies support the latter paradigm more than the former.

The factors that determine whether a patient with NAFLD also develops necro inflammatory changes and fibrosis are not known.

Possibilities include genetics, dietary composition, and concomitant forms of other liver disease (e.g., chronic hepatitis C). There may be important racial and ethnic predispositions, but these remain poorly characterized at this time.

Predictors of NASH and advanced fibrosis:

HAIR score

1. Hypertension

2. Alanine transaminase (ALT) > 40 IU/l

3. Insulin resistance (IR) index > 5

Presence of 2 or all 3 factors predict NASH.

BAAT score

1. Body mass index (BMI) > 28 kg/m2

2. Age > 50 yrs

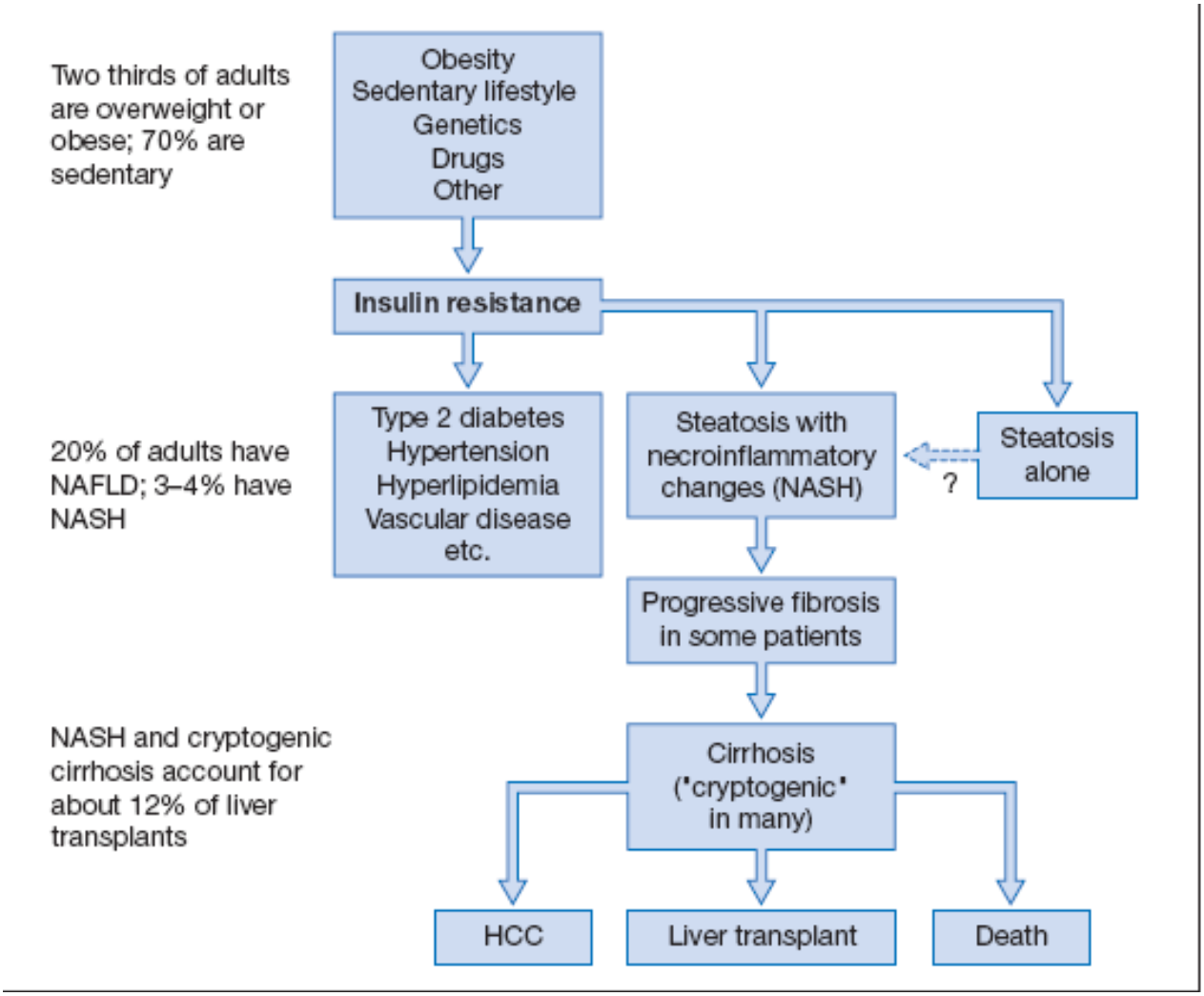
3. ALT > 2-fold rise

4. TG > 1.7 mmol/l

Presence of none or only 1 factor rules out the possibility of fibrosis or cirrhosis.

PATHOGENISIS

The pathogenesis of NASH is unknown. In 1998,James first proposed the‘two hit’ hypothesis for pathogenesis NASH. Fatty liver,the earliest and most prevalent stage of NAFLD is thought to sensitize the liver to additional necro inflammatory insults, thus promoting disease progression to steatohepatitis, cirrhosis and hepatic failure. A number of factors point to multi factorial nature of this disease, including derangement in metabolic parameters, endotoxin-induced cytokine release and oxidative stress. After absorption from the intestines, fat is carried to the adipose tissue for storage in the form of triglycerides. It is released as free fatty acids (FFA) when the body is deprived of food or under the effect of certain hormones/ drugs (such as epinephrine, corticosteroids). FFA are carried to the liver bound to albumin. After entering the hepatocytes they are either oxidized to produce energy.



Insulin resistance

This is the first hit hypothesis in the pathogenesis of NAFLD

The association between the severity of insulin resistance/ presence of NIDDM, and the risk of NASH can be explained by peripheral insulin resistance increasing the supply of FFA to the liver and by hepatic insulin resistance favouring the development of oxidative stress. A central abnormality in the pathogenesis of steatosis appears to insulin resistance resulting in lipolysis, which

increases circulating free fatty acids which are then taken up by the liver as an energy source. The fatty acids overload the hepatic mitochondrial ß-oxidation system, leading to accumulation of fatty acids in the liver Indeed, some investigators suggest NAFLD to be the hepatic manifestation of the insulin resistance syndrome29. NAFLD does not universally progress to NASH, and the precise pathogenesis of steatohepatitis is yet to be determined.

However, dysregulation of peripheral lipid metabolism seems to be important. There is a strong association between non alcoholic fatty liver and features of the metabolic syndrome, suggesting a simultaneous insulin resistance and decreased sensitivity to leptin.Leptin may have a role in the regulation of fat deposition, fibro genesis, and inflammation in patients with NAFLD.6 Obese patients with insulin resistance have decreased serum adiponectin and increased serum resistin .

Cytokines and NASH

Cytokines are attractive candidates for the ‘second hit’ in the pathogenesis of NASH. They are capable of producing all the classical histological features of NASH, including hepatocyte death/apoptosis (TNF-*a*), neutrophil chemotaxis (IL-8) and hepatic stellate cell activation (TNF-*a*, TGF-b) . There is evidence that endotoxin-mediated cytokine release is important in the occurrence of hepatic steatohepatitis and that the use of antimicrobial therapy may be able to

prevent or reverse its development. In addition, it has been shown that patients with NASH had an increased expression of TNF-*a* mRNA both in their liver and adipose tissue compared to obese controls, and this over-expression correlated with histological severity. Lipid metabolism is, in part, regulated by adipokines, including tumor necrosis factor (TNF) and adiponectin. TNF-, which interferes with insulin signaling thereby favoring steatosis, is elevated in fatty liver disease albeit not specific to type 2 diabetes[29]. TNF- is also pro inflammatory and, thus, may play a role in the pathogenesis of the inflammation in NASH[30] . Adiponectin, in contrast to TNF-, is anti lipogenic and anti-inflammatory and, thus, may protect the liver from lipid accumulation and inflammation. Adiponectin levels are decreased in conditions associated with NAFLD, including insulin resistance[28] obesity[29],type 2 diabetes , and NAFLD[29]. Adiponectin and TNF- therefore have opposing effects. The net effect of increased TNF- and decreased adiponectin is prosteatotic and pro inflammatory. This low level of adiponectin expression may predispose patients to the progressive form of NAFLD

Oxidative stress and lipid per oxidation

There is growing evidence implicating FFA in the production of oxidative stress within hepatocytes. Increased fatty acid *b*-oxidation as well as peroxisomal fatty

acid oxidation can both lead to increase in reactive oxygen species generation and subsequent lipid per oxidation. In the fasting state, patients with NAFLD have increased plasma levels of *b*-OH butyrate[49]

Under normal conditions, hepatic aerobic metabolism involves a steady-state production of pro-oxidants such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are balanced by a similar rate of their consumption by antioxidants. Imbalance in the pro-oxidant/ antioxidant equilibrium in favour of pro-oxidants constitutes the oxidative stress phenomenon, a condition that may induce a number of patho physiological events in the liver. Hepatotoxicity by oxidative stress may be achieved through a direct attack of ROS and RNS on essential biomolecules with loss of their biological functions and cell viability .

Alternatively, ROS may indirectly activate redox sensitive transcription factors such as nuclear factor *k*B (NF-*k*B)[50] or activator protein-1 (AP-1)[51] , thus triggering the production of cytotoxic, pro inflammatory and/or fibrogenic mediators by Kupffer cells and other non parenchymal cells. . These studies suggest that chronic oxidative stress may be important in the progression of fatty liver Pessayre *et al*[52] have shown that excess fat deposition in the liver is associated with lipid per oxidation and the degree of this per oxidation is directly

related to the severity of steatosis. The end-products of lipid per oxidation, 4- hydroxynoneal and malondialdehyde, covalently bind to hepatic proteins, and act as potent agents for neutrophil chemotaxis and stimulating pro-inflammatory cytokines. Malondialdehyde also activates hepatic stellate cells to produce collagen, leading fibrosis

Other factor

In addition to obesity and insulin resistance, some other environmental or genetic factor(s) is required for the progression of NASH. Studies in leptin-deficient ob/ob mice which have profound insulin resistance and dramatic hepatic steatosis without steatohepatitis or fibrosis, suggests that leptin may in fact have a role in promoting hepatic fibrogenesis, directly by an autocrine effect on hepatic stellate cells and indirectly by up-regulating the production of TGF-*b* from sinusoidal endothelial cells and Kupffer cells . The association of hepatic iron accumulation and NAFLD continues to be debated. While some studies have found that 22 to 62% of individuals with fatty liver disease have evidence of iron overload, other have failed to show such relationship[53] .In another study, a higher incidence of the HFE mutation (Cys282Tyr) was reported.

Candidate genes

NASH and cryptogenic cirrhosis study suggest that genes might play an important role in NAFLD. Different types of candidate genes of NAFLD as follows: genetic factors related to insulin resistance, FFA supply and lipid metabolism.

Apo lipoprotein E, a regulator of lipoprotein metabolism, was included and considered to be of great importance. Genes associated with the 'second hit', include (i) genes encoding proteins involved in the severity of oxidative stress such as HFE (haemochromatosis gene), CYP2E1, CYP4A; (ii) genes encoding cytokines and their receptors; (iii) genes related to adverse effects of FFA such as transcription factors, peroxisome proliferator-activated receptors (PPARs). Among these candidate genes are: (a) leptin and its receptor, which are related to obesity, insulin resistance, increased FFA synthesis and reduced FFA oxidation; (b) PPAR regulating a variety of genes encoding enzymes involved in FFA oxidation and oxidative stress; and (c) PPAR which up regulates UCP2 (un-coupling protein C) and inhibits leptin gene expression and macrophage function.

NASH is now conceptualized as encompassing at least three components among the tetrad of steatosis, hepatocellular injury, focal mixed cell-type inflammation and fibrosis. NASH is characterized by zone-3 dominant hepatic

steatosis with ballooned hepatocytes and Mallory bodies, zone-3 peri-cellular and peri-venular fibrosis with or without bridging fibrosis, and lobular inflammatory cell infiltration[6] Liver disease has not been associated with type 1 diabetes mellitus, which reflects the current understanding that insulin resistance, not insufficiency, is associated with this type of liver disease.[7,8] Further proof for the association of liver disease with diabetes comes from the Insulin Resistance Atherosclerosis Study (IRAS), which showed that liver function markers like the Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) are predictors of incident diabetes[9] An Italian study showed that 10.5% of the subjects who had elevated AST and ALT had diabetes.[9] A similar study in Cleveland showed that nearly 33% of subjects with NASH had diabetes.[10]

There are several histological stages in the progression of NAFLD to cirrhosis. The earliest stage is a simple fatty liver alone. Over time, steatohepatitis may become associated with increasing fibrosis. Eventually, cirrhosis may develop. Cirrhosis secondary to NASH may also be complicated by the development of hepatocellular carcinoma..

CLINICAL FEATURES

Most patients of NAFLD (45 - 100%) have no symptoms or signs of liver disease at the time of diagnosis .

In these patients, abnormal liver function tests are often discovered incidentally. When symptoms occur, they are non-specific – like

persistent fatigue (50 - 73%), pruritus (0 - 6%), oedema (2 - 10%), malaise, and right upper quadrant discomfort or pain8.

Other features like GI bleeding (0 - 3%), jaundice (0 - 5%), ascites (0 - 3%), pruritus, and oedema point towards severe liver disease. Ascites, hepatic encephalopathy, and variceal bleeding indicate cirrhosis of liver due to progressive NASH.

When the disease is not advanced, diffuse non-tender smooth hepatomegaly is present in 25 - 53% of patients. Such patients are usually obese and/or diabetic.

Advanced disease may present with right hypochondrium tenderness, jaundice, palmar erythema, spider angioma, portal hypertension, ascites, varices, and splenomegaly.

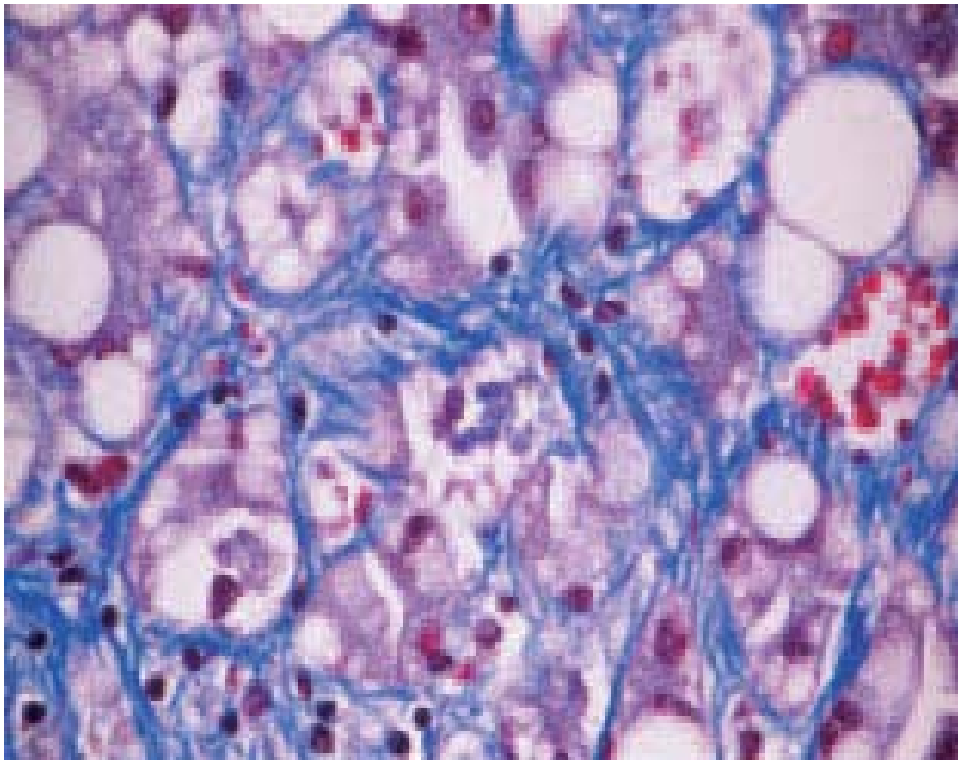
DIAGNOSIS

Diagnosis of NAFLD is based on two criteria: (i) establishing the presence of a fatty liver or steatohepatitis, and (ii) establishing the nonalcoholic nature of the disease process. Radiologic imaging of the liver with sonography, compute tomography (CT), or magnetic resonance imaging (MRI) has an adequate threshold for detection of fatty infiltration of the liver, used either singly or in combination. Each of these modalities has its own pitfalls and cannot distinguish steatosis from steatohepatitis. These methods are also insensitive in detecting steatosis of less than 25%

Liver biopsy is the gold standard for diagnosis of NAFLD/NASH for the following important reasons: (i) to confirm diagnosis and establish severity of fibrosis and presence of cirrhosis, and (ii) to exclude other coexisting conditions that can result in hepatitic steatosis. However, ethical consideration as well as inherent risk associated with this procedure limit its widespread applicability.

Histological diagnosis of steatohepatitis relies on a constellation of lesions that include steatosis (mainly macrosteatosis, occasionally microsteatosis), ballooning of hepatocytes (hepatocyte injury), perisinusoidal fibrosis and a mixed lobular inflammatory infiltrates[55]. Currently, minimal

histological criteria required for diagnosis are the presence of steatosis and intra lobular necrotic inflammatory reactions[54].



Tri chrome stain shows blue staining fibrosis around swollen hepatocytes.

The ALT/AST ratio is usually less than one. Imaging studies may help with diagnosing fatty infiltration of the liver, but they do not help in distinguishing between fatty liver, steatohepatitis, and steatohepatitis with fibrosis.[11]

Grading and stages of NAFLD[56] .

Grade of NAFLD

Macro vesicular steatosis

Grade 0: No steatosis

Grade 1: < 33% steatosis

Grade 2: < 33–66% steatosis

Grade 3: > 66% steatosis

Necro inflammatory activity

Grade 1 (mild) steatosis up to 66%; occasional ballooned hepatocyte (mainly zone 3); scattered intra-acinar neutrophil (PMN) lymphocytes, no or mild portal inflammation.

Grade 2 (moderate) steatosis of any degree; obvious zone 3 ballooning degeneration; intra-acinar PMNs; zone-3 peri sinusoidal fibrosis may present mild to moderate, portal and intra-acinar inflammation.

Grade 3 (severe) pan acinar steatosis; widespread ballooning; intra-acinar inflammation; PMNs associated with ballooned hepatocyts, mild to moderate portal inflammation.

Stage of NAFLD

Stage 1: zone 3 perisinusoidal/pericellular fibrosis; focally or extensively present.

Stage 2: zone 3 peri sinusoidal/peri cellular fibrosis with focal or extensively peri portal fibrosis.

Stage 3: zone 3 peri sinusoidal/peri cellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis.

Stage 4: cirrhosis

TREATMENT STRATEGIES

Currently, there are no effective therapies for NASH, as its natural history and prognosis are not well understood. Treatment of patients with non-alcoholic fatty liver has typically been focused on the management of associated conditions such as obesity, diabetes mellitus, and hyper lipidemia as well as discontinuation of potentially hepatotoxic drugs

. Appropriate metabolic control for patients with diabetes mellitus or hyper lipidemia is recommended, but is not always effective in reversing non-alcoholic fatty liver associated with obesity may resolve with weight reduction,, although the benefits of weight loss have been inconsistent. On the other hand, striking weight losses have also been associated with progression of the disease. Moderate and gradual weight loss can safely improve in chronic liver disease associated with obesity and diabetes. Rapid weight loss may aggravate the histological lesions of steatohepatitis . A weight loss of 500 g per week in

children and 1600 g per week in adults is recommended, although the most appropriate rate of weight loss is still to be established in fatty liver.

A number of pharmacologic agents have been shown to be promising in the treatment of NASH . Promising results of pilot studies evaluating ursodeoxycholic acid, gemfibrozil, betaine, *N*-acetylcysteine and alpha-tocopherol suggest that these medications may be of potential benefit in the treatment of patients with nonalcoholic fatty liver, but need further study in controlled trials. The association of hyperinsulinemic insulin resistance has provided a target for treatment. Metformin, a biguanide that reduces hyperinsulinemia and improves hepatic insulin resistance has been shown to greatly reduce hepatomegaly and steatosis in mice and may potentially be useful in the treatment of NASH in humans.

Study by Department of clinical biochemistry (2008) by sandya Sharma,dharmveer et all in SMS college Jaipur showed that (Indian) journal clinical biochemistry,2008/23) Subject with NAFLD were more obese, dyslipidemic and glucose intolerant. Almost 70% subjects with NAFLD had metabolic syndrome which is five and half fold higher than those without NAFLD. Results of the present study supports the hypothesis that the insulin resistance is a key factor in Metabolic syndrome, plays a pivotal role in the patho

physiology of NAFLD[57] as subjects with NAFLD were insulin resistant and prevalence of NAFLD was significantly higher in those with metabolic syndrome.Thus,fatty liver can be considered as hepatic consequence of metabolic disease leading to increase prevalence of NAFLD

MATERIALS AND METHODS

Materials and methods

This study was done at the Diabetology Clinic of Coimbatore Medical College and Hospital, Coimbatore.

One hundred and eighteen type 2 diabetic patients diagnosed according to the American Diabetic Association criteria, newly diagnosed or on follow- up were included in the study.

.Random selection was done using random number charts.

Patients with history of any chronic drug intake other than oral hypoglycemic drugs, jaundice or alcohol intake, HBsAg positive were excluded from the study.

An informed consent was taken. The study protocol was approved by the Ethics committee of Coimbatore Medical College Hospital.

The type of oral hypoglycemic drug intake, height and weight were recorded and Body Mass Index (BMI) calculated.

Patients were subjected to biochemical investigations to detect the liver enzyme levels, serum bilirubin, serum albumin, serum globulin, serum total proteins and total cholesterol. Serum albumin levels of 3.5 -5.5 mg%, serum globulin of 2-

3.5mg%, AST of 0 – 35 IU/L, ALT of 0 – 35 IU/L, Bilirubin levels of 0.3-1 mg%, total cholesterol less than 200mg%, serum total proteins of 5.5-8mg%, fasting glucose less than 130mg% and a 2hr post prandial glucose of less than 180mg% were taken as normal . Their most recent fasting and post-prandial blood glucose values were recorded to asses the control of diabetes.

Fifty two patients were subjected for ultrasonographic examination by a qualified radiologist who was masked from the patient's diagnosis or the indication for ultrasound, to assess the liver parenchyma, liver size, gall bladder, biliary and portal system.

The echo texture of the liver parenchyma was graded as follows

***Grade 1*:** A slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders.

***Grade 2*:** A moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm.

***Grade 3*:** A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver.[12]

We used ultrasonography to detect liver changes since this method is sensitive in detecting fatty liver, is cheap, minimally invasive and easy to perform, and ensures patient compliance. It has been shown that attenuation coefficient of the

liver on ultrasound increases as the amount of fat in the liver increases, though the same is not true for fibrosis. However, this method does not allow for quantification of fat infiltration.[13]

The data was analyzed and statistical conclusions drawn using the SPSS 13.0 software.

ANALYSIS OF RESULTS

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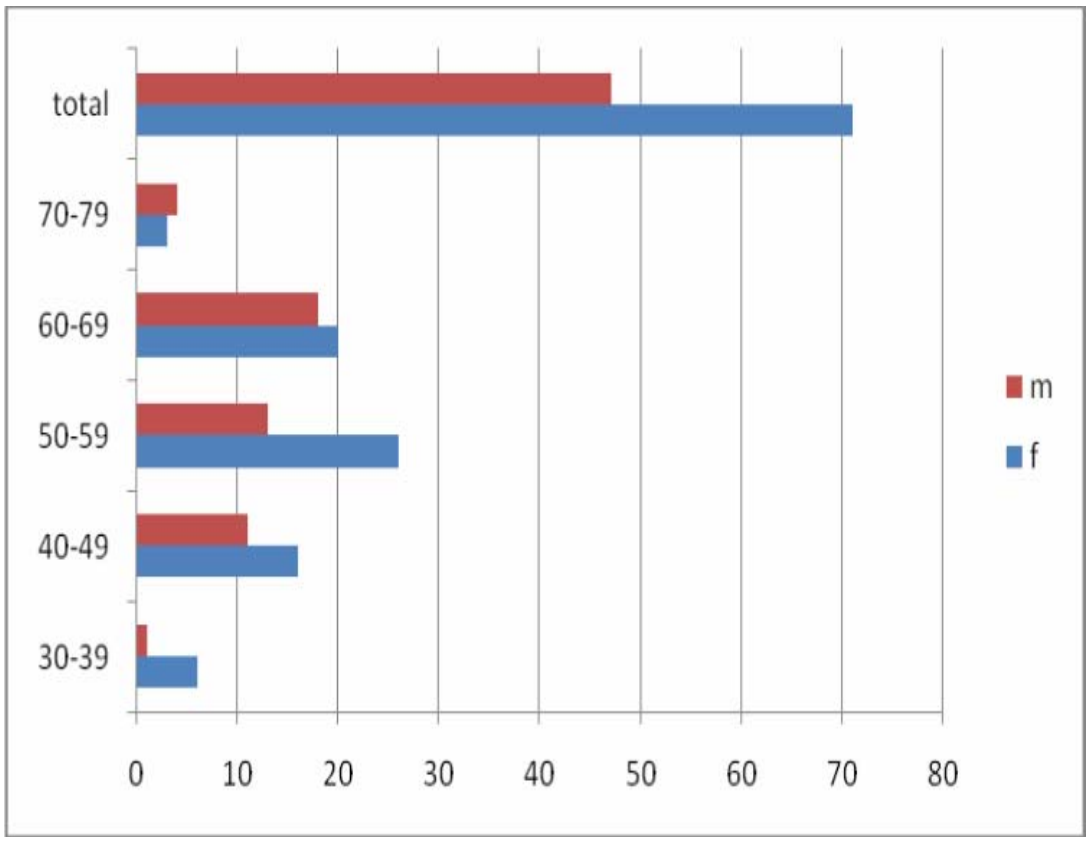
A total of one hundred and eighteen patients were included in the study, 71(60.2%) females and 47(39.8%) males. The age and sex distribution is shown in table no: 1.

Table No: 1 Age and Sex distribution

Age Class	Sex			
	Female		Male	
30-39	6	85.7%	1	14.3%
40-49	16	59.3%	11	40.7%
50-59	26	66.7%	13	33.3%
60-69	20	52.6%	18	47.4%
70-79	3	42.9%	4	57.1%
Total	**71**	**60.2%**	**47**	**39.8%**

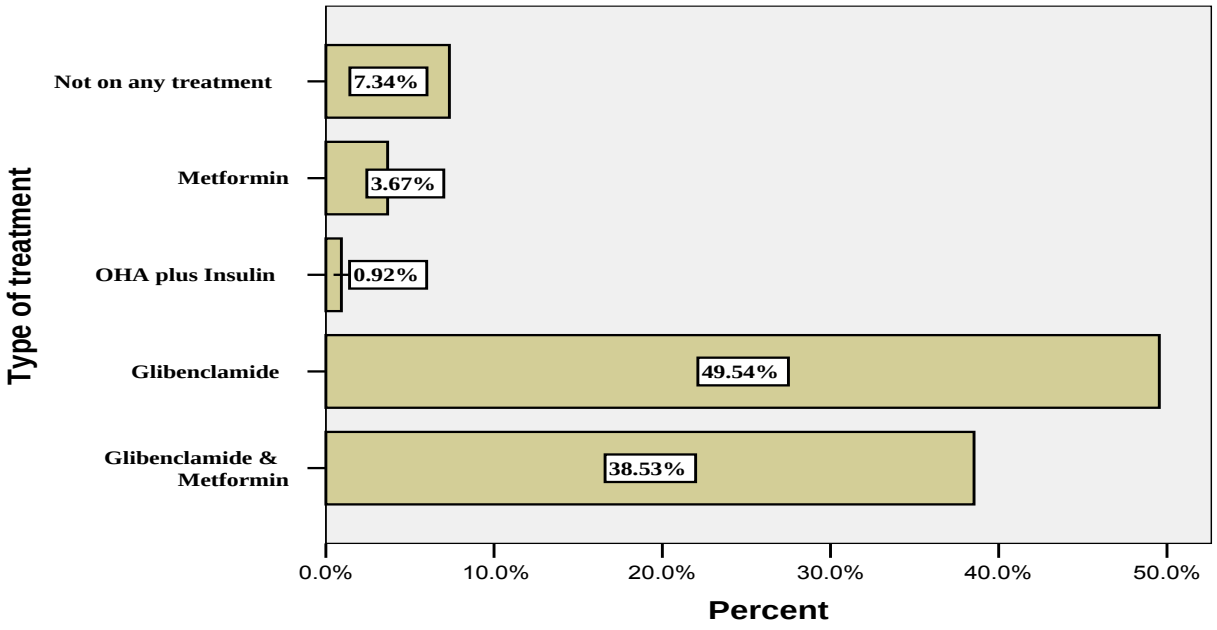


Eleven (9.3%) cases were newly diagnosed during the course of the study. Sixty six (55.9%) cases had diabetes for duration less than 5 years. Forty one (34.7%) cases had diabetes for a duration more than or equal to 5 years.

One hundred and eleven patients were on oral hypoglycemic drugs, including 2 patients who were additionally on plain insulin injections. Majority of the patients were either on glibenclamide alone or combination of both glibenclamide and metformin. Eight patients though diagnosed to have diabetes were not on any drugs at the time of presentation. The dosages they were on

ranged from 2.5mg to 10 per day for glibenclamide and 500 mg to 3000 mg per day for metformin.

Fig 1 Type of Antidiabetic treatment



Results of the biochemical investigations are on table. 2

Table No: 2 Biochemical Investigations

Investigation	Mean(SD)	Maximum	Minimum
STP	7.0(0.4)	7.9	6.0
Serum Albumin	4.1(0.4)	4.8	2.4
Serum Globulin	2.9(0.4)	3.7	1.2
Serum Bilirubin	.9(0.3)	2.1	.4
AST	23(8)	60	12
ALT	19(8)	55	10
ALP	114(38)	211	30
Fasting Blood Glucose	139(46)	250	70
Post prandial Blood Glucose	210(55)	330	110
Total Cholesterol	231(34)	328	197

The total serum proteins were within the normal range for all the patients with a mean value of 7.03 +/- 0.4. low albumin levels, taken as less than 3.5

mg% were found in 4 (3.4%) patients and low globulin level, taken as less than 2 mg% in 2 (1.7%) patients.

Liver function tests revealed an elevated AST levels taken as more than 35 IU/L in 8 (6.8%) patients and an elevated ALT levels taken as more than 35 IU/L in 5 (4.2%) patients. An AST/ALT ratio of more than 1 was found in 101 (85.6%) patients. Alkaline phosphatase levels were above 120 IU/L in 37 (31.4%) patients.

Age-wise and Sex-wise comparison of the liver function tests (Tables 3&4) revealed no significant difference between the various age classes or between sexes.

Table No: 3 Age wise comparison of mean value of Liver function tests

Test	Age class				
	30-39	40-49	50-59	60-69	70-79
STP	7.0	7.0	7.0	7.1	7.0
S.Albumin	4.0	4.3	4.0	4.0	4.3
S. Globulin	2.9	2.9	2.9	2.9	2.9
S. Bilirubin	.9	.9	.8	1.0	1.2
AST	23	22	22	23	31
ALT	19	19	19	20	25
ALP	110	127	110	109	119

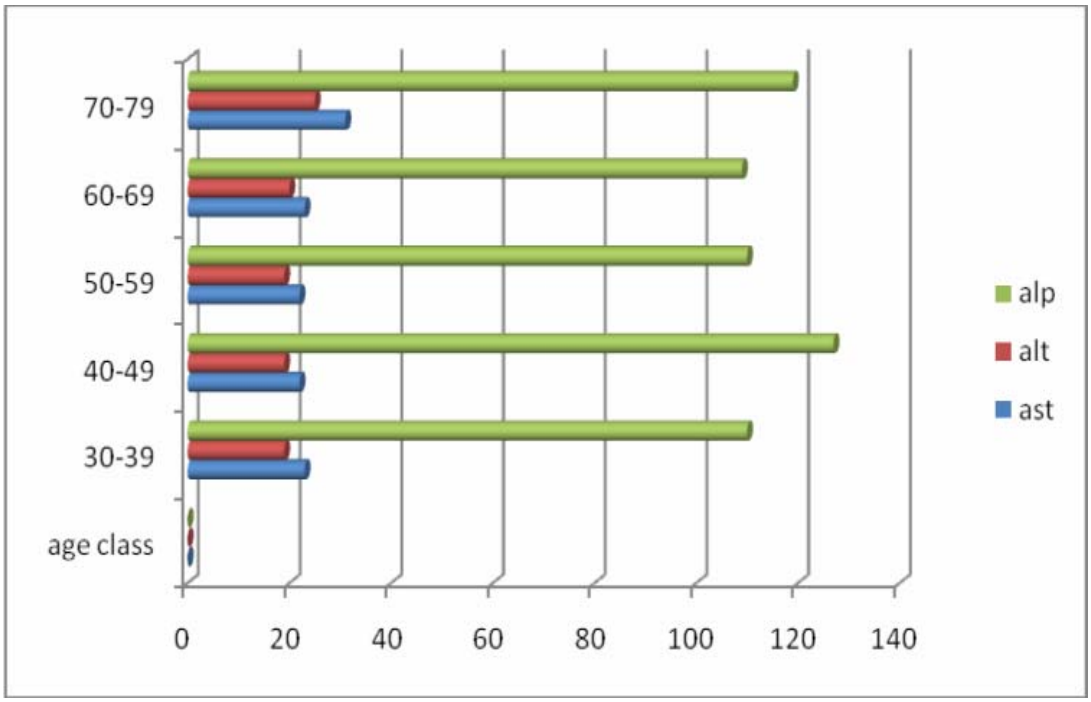
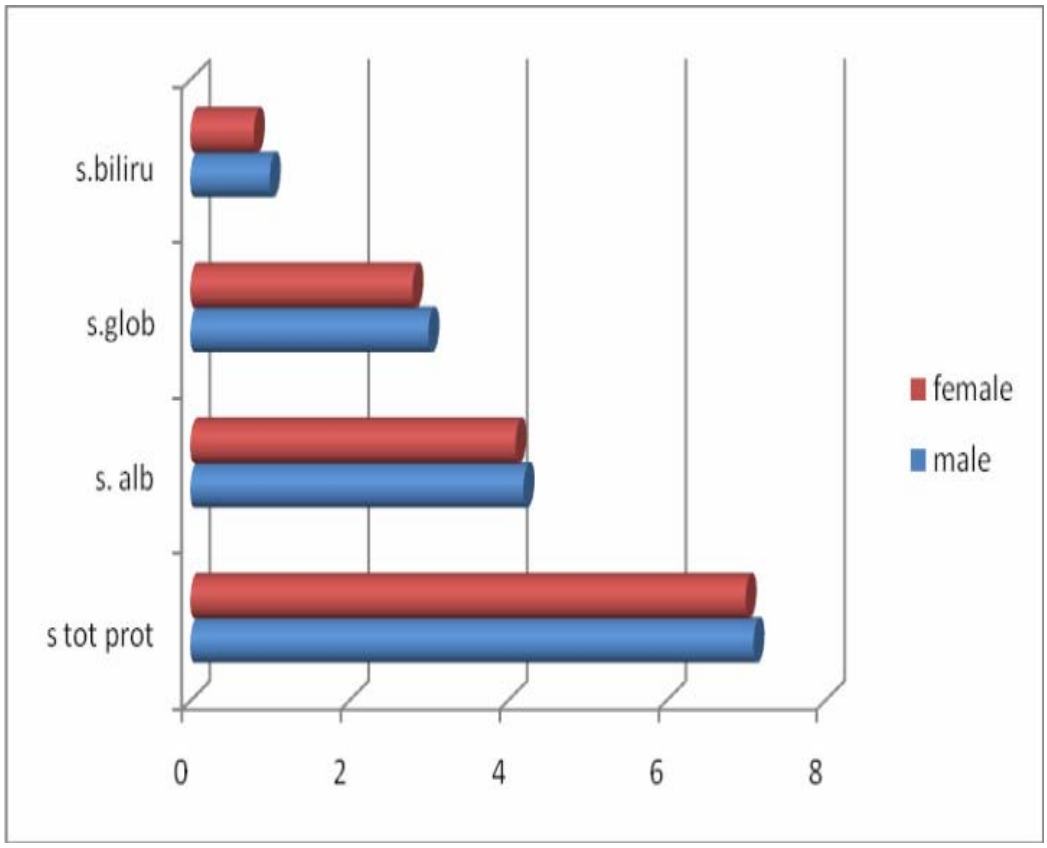


Table No: 4 Sex wise comparison of Liver function tests

Investigation	Sex	
	Female	Male
STP	7.0	7.1
Serum Albumin	4.1	4.2
Serum Globulin	2.9	3.0
Serum Bilirubin	0.8	1.0
AST	22	24
ALT	19	20
ALP	114	114



Among the patients whose recent fasting and 2 hr post prandial blood glucose values were available, 47 percent had a fasting glucose more than 130 mg% and 61% had a 2 hr post prandial glucose more than 180mg%. There was no significant difference between mean values across gender or age classes.

Body mass index measurements revealed that 25 (35.2%) women were over weight (BMI>25) and 5 (7.0%) were obese (BMI>30). The numbers of overweight men were 12 (25.5%). No male patient was found to be obese.

Ultra sonographic examination was done in 52 patients, fatty liver was found to be more common in females. Overall 23 patients (42.3%) had fatty liver out of the 52 patients screened. Sex wise and BMI class wise distribution is given in tables 5 & 6. Hepatomegaly was identified in 5 (9.6%) patients of whom 4 were males. Asymptomatic gall stones were found in 5 (9.6%) patients, 3 females and 2 males. Bile duct was found to be dilated (>5mm) in 6 patients, portal vein was normal (<12mm) in size in all the patients

Table No: 5 Sex distribution of fatty liver

Fatty Liver	Sex	
	Female (%)	Male (%)
Grade 1 fatty liver	13(50)	8(30.8)
Grade 2 fatty liver	2(7.7)	0(0)
No fatty change	11(42.3)	18(69.2)

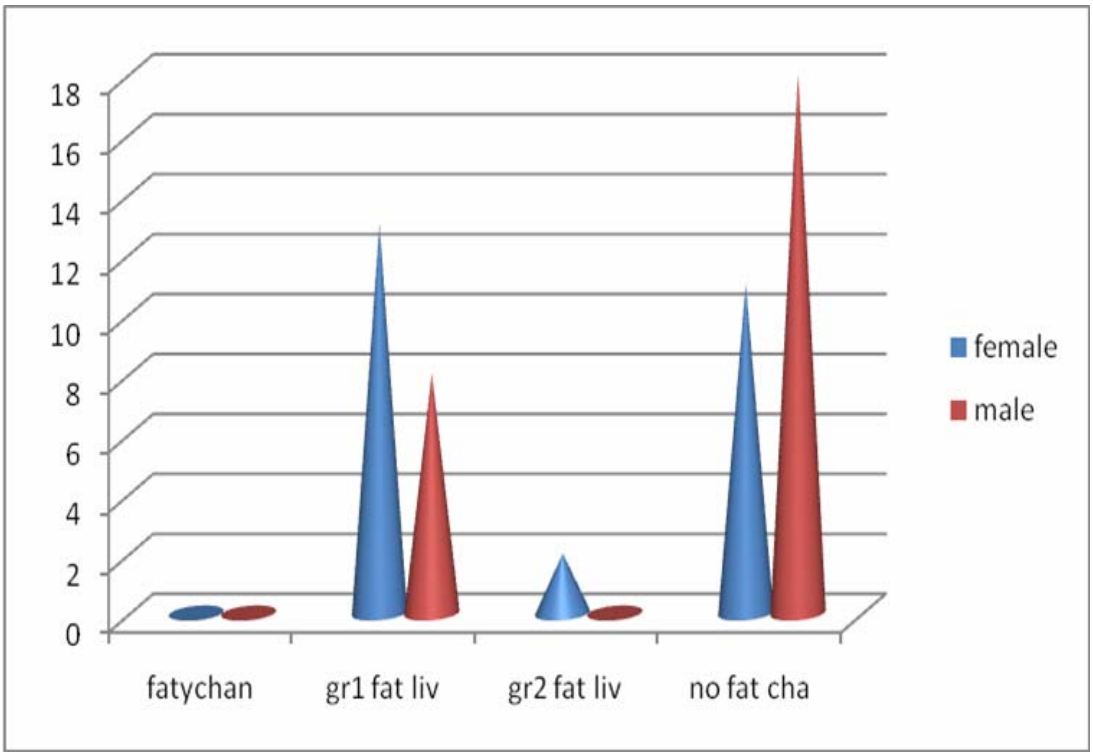
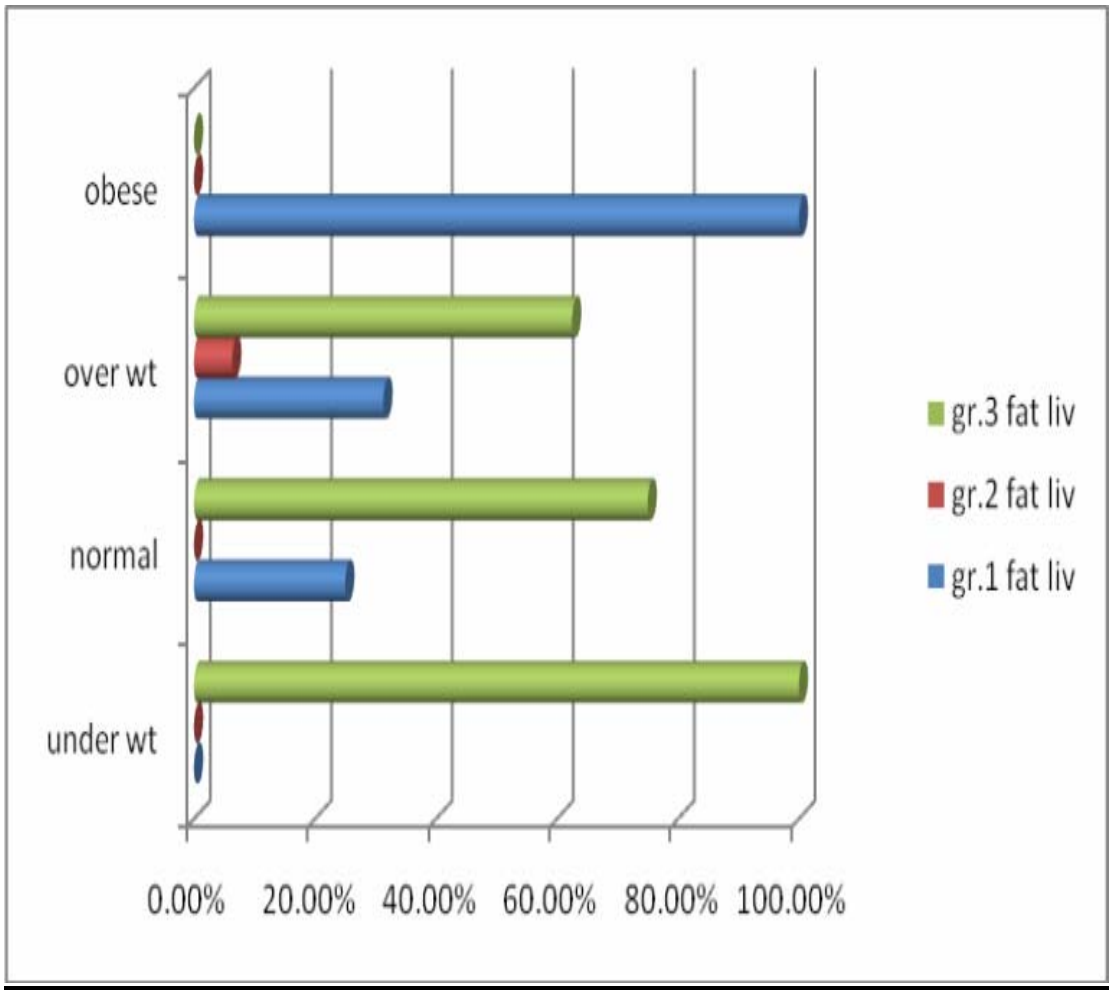


Table No: 6 BMI Class wise distribution of fatty liver

Fatty Liver	BMI Class				
	Underweight	Normal	Overweight	Obese	Morbid Obesity
Grade 1 fatty liver	.0%	25.0%	31.3%	100%	.0%
Grade 2 fatty liver	.0%	.0%	6.3%	.0%	.0%
No fatty change	100.0%	75.0%	62.5%	.0%	.0%


obese
over wt
normal
under wt
0.00%
20.00%
40.00%
60.00%
80.00%
100.00%
gr.3 fat liv
gr.2 fat liv
gr.1 fat liv

DISCUSSION

DISCUSSION

Since clinical symptoms of fatty liver are nonspecific or silent this study does not attempt to define the clinical symptoms of fatty liver. Fatty liver most commonly affects middle-aged women with obesity, altered glucose metabolism, hyper lipidemia, and hypertension.

Age, Gender and Obesity

As reported by Kelly et all[28] there was no difference in the mean age of patients with fatty liver as compared to those with normal liver. Sixty five percent of the patients with fatty liver in this study were females but no significant difference(p value>0.05) in proportion based on gender was found in those with grade 1 fatty liver compared to those without evidence of fatty liver. Obesity was found to have a significant association with fatty liver, in the current study 70% of patients with grade 1 fatty liver had a BMI more than 25 and both patients with grade 2 fatty liver were overweight.

Liver enzymes

Reid etal[14] and Dixon et al[15] found elevated AST levels in patients with NASH. Laboratory abnormalities identified included a 2-4-fold elevation of serum amino transferase levels while other liver function test results were normal. Agarwal etal[16] and Kelly et al[28] documented elevation of ALT as the biochemical abnormality in patients with NASH. A recent study found that patients with NASH and those with higher grade of histological inflammation had increment of transaminases and albumin levels . The same study showed a correlation of fibrosis with AST and ALT levels. Elariny etal showed that while ALT was associated with NASH and advanced fibrosis, the majority of the patients with either NASH or advanced fibrosis had normal AST.[13] An AST/ALT ratio >1.0 was yet another finding in a study on NASH[15].

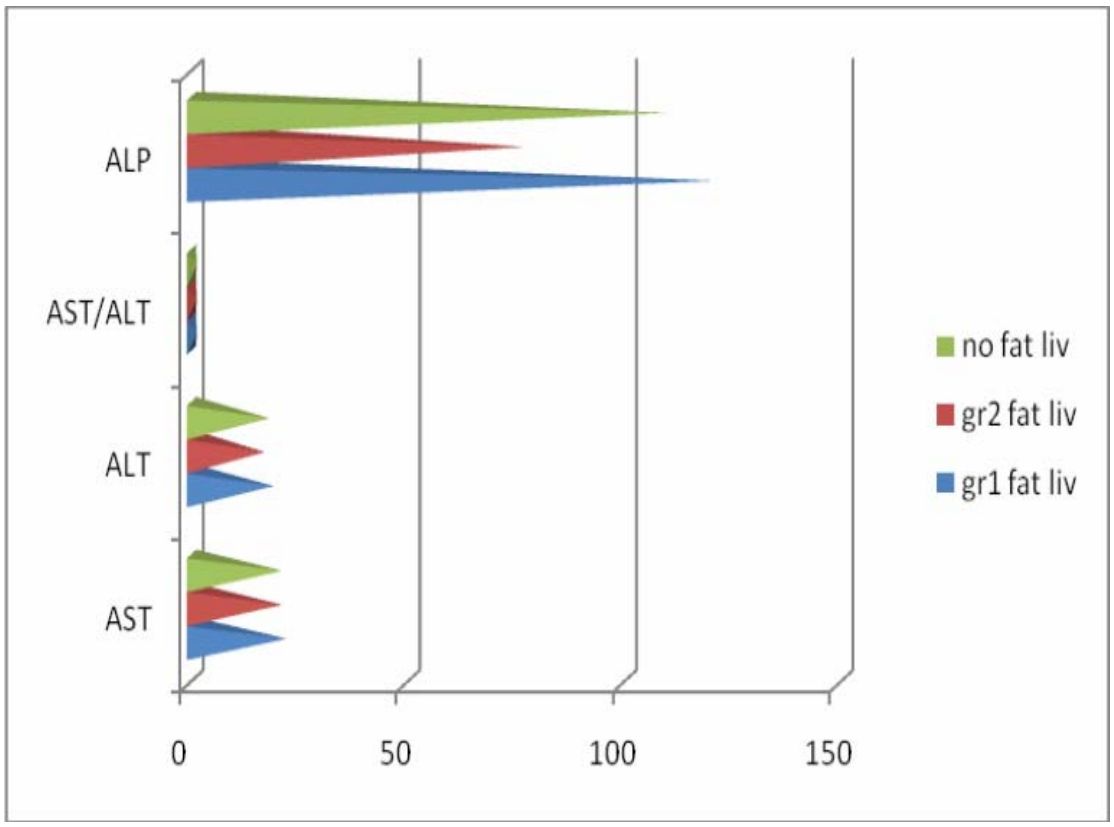
Contrary to all these a study in 2003 found liver enzymes to be insensitive and unreliable to confirm the diagnosis or stage the extent of fibrosis. Older age, obesity, and diabetes were shown to be predictive of fibrosis.

Our study also did not find a significant elevation of any of the liver enzymes. There was no statistically significant difference (p value >0.05) between the parameters among patients with grade 1 fatty liver and those without fatty liver (table no: 7). Eighty five percent of the patients in this study had

AST/ALT ratio more than one, but it was not found to have any association with fatty liver.

Table No: 7 Liver enzymes in patients with fatty liver

Enzyme	Grade 1 fatty liver	Grade 2 fatty liver	No fatty change
AST	22	21	21
ALT	19	17	18
AST/ALT	1.2	1.2	1.2
ALP	121	77	110

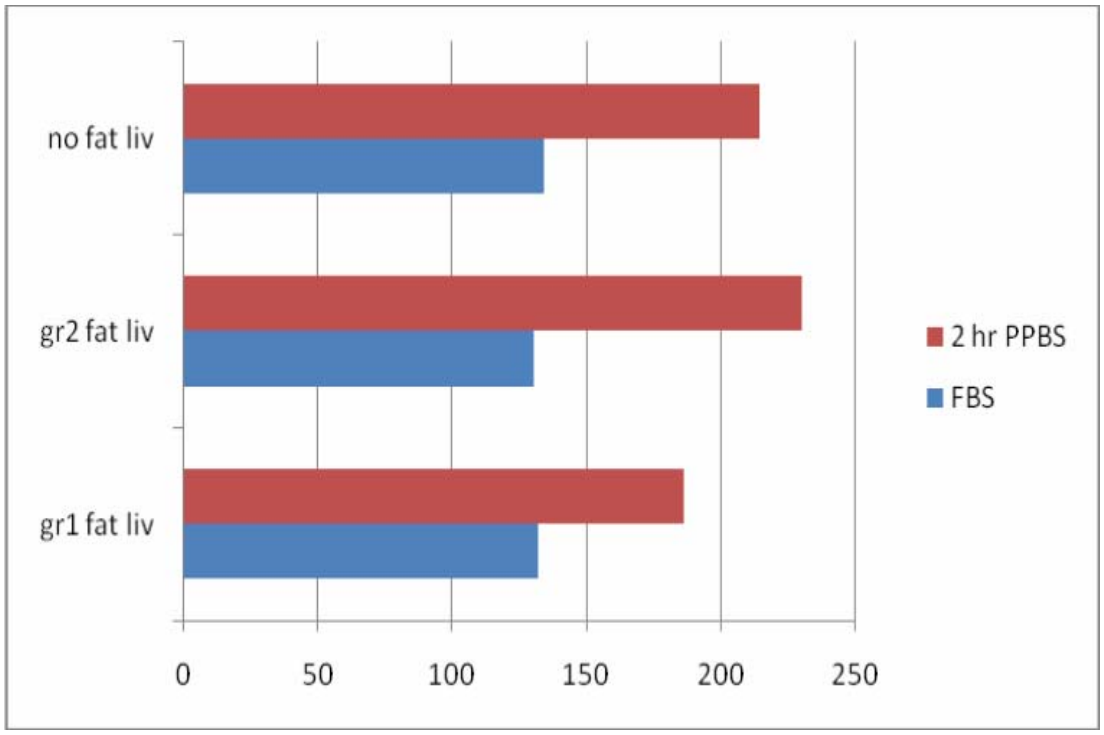


Insulin resistance

Obesity, insulin resistance, and increased concentrations of plasma fatty acids are considered to increase the risk for fatty liver, and each of these metabolic factors is also characteristic of type 2 DM[29.] It has been reported that fatty liver in turn influences severity of hepatic insulin resistance in type 2 DM. Among nonobese men without type 2 DM, fatty liver was found to correlate with hepatic insulin resistance independently of obesity and intra-abdominal adiposity[28]. Volunteers with type 2 DM and fatty liver were substantially more insulin resistant than those with type 2 DM but without fatty liver and had higher levels of plasma free fatty acids and more severe dyslipidemia[30.] The present study did not measure insulin resistance but comparing the mean blood glucose values between those with or without fatty liver did not reveal any significant difference (p value >0.05) (Table no: 8)

Table No: 8 Mean Fasting and Post prandial blood glucose in Patients with fatty liver

Blood Glucose	Grade 1 fatty liver	Grade 2 fatty liver	No fatty change
Fasting	132	130	134
2 Hr Post prandial	186	230	216



Hyperlipidemia

Fatty acid flux to the liver has been postulated as an important factor in the pathogenesis of fatty liver and is also an important determinant of the synthesis and secretion of triglyceride-rich lipoproteins[29]. It is possible, therefore, that hepatic steatosis may influence the severity of dyslipidemia in type 2 DM. Hypertriglyceridemia is more severe in individuals with fatty liver. Only the total cholesterol levels were assayed in our study. A comparison of the mean total cholesterol levels between the fatty liver group and the rest did not reveal any statistically significant difference.

Treatment

Patients with diabetes should have their disease controlled appropriately. Since NAFLD is associated with insulin resistance, the use of insulin-sensitizing agents may be logical. The thiazolidinediones (e.g. pioglitazone) improve peripheral insulin sensitivity. A small study of patients treated with troglitazone showed improvement in mean ALT levels and in hepatocellular inflammation. Metformin has been shown to improve serum aminotransferase levels.

However, there are no definitive data on the use of these drugs in the treatment of NAFLD[12]. The risks of hepatotoxicity associated with these agents have not yet been well characterized in this populations In a recent randomized

controlled trial, metformin was found to be superior to vitamin E in terms of normalization of ALT[31.]

A significant reduction in all the liver enzymes was observed after Essentiale treatment[32] Essentiale is prepared from Soya beans, and has phosphatidylcholine as its active ingredient. Some studies have explored the efficacy of glitazones, vitamin E, probucol, atorvastatin and alternative therapies like betaine, and have shown some beneficial results[33,34,35,36]

Based on the results of the study by Osei-Hyaiman et al, the hepatic Endocannabinoid system may be a target for the treatment of nonalcoholic steatohepatitis (NASH)[37]

Currently, treatment is focused on modifying risk factors such as obesity, diabetes mellitus, and hyperlipidemia. Antioxidants such as vitamin E, N-acetylcysteine, betaine, and others may be beneficial in the treatment of NASH. [17]

CONCLUSION

CONCLUSION

The increasing prevalence of fatty liver in diabetes is well established.

There is an increasing understanding about its aeti pathogenesis, and its various pathological stages have been well defined.

It is important to acknowledge that the increased incidence of steatohepatitis and hepatic fibrosis in type 2diabetes may translate into increased incidence of hepato cellular carcinoma.

Liver biopsy though the gold standard for the diagnosis and staging of the disease, cannot be used for large scale screening. More non invasive methods are the need of the hour for early and wide screening to detect this disease.

Liver enzymes were thought to be a potential non invasive strategy for early detection of this disease, but the present study did not find any correlation of the level of liver enzymes and the degree of fatty liver in Indian patients.

so the conclusion is less expensive non invasive USG of liver will be the ideal diagnostic tool which is also well trained operator dependant can definitely help to detect early fatty liver in patients with diabetes

The moral of study is force is needed for all physicians to study and practice with USG as bed side diagnostic tool for management and follows up study of type 2 diabetes mellitus patients.

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MASTER CHART

Sl No	Name	Age	Sex	OP No	Duration	glibenclamide	Metformin	Insulin	Weight	Height	BMI	STP	S.ALB	S.GLOB	S.BIL	AST	ALT	AST/ALT	ALP	FBG	PPBG	T.CHOl	Fatty change	Size	Gall bladder	Bile ducts	Portal vein
1	r sumathi	39	f	4571	0	1	1	0	51	152	22.1	7.2	4.1	3.1	1.4	28	24	1.17	103	210	250	168					
2	mohammed usuf	60	m	2410	0	0	0	0				7.2	3.6		1.2	25	23	1.09	103	175	211		n	n	n	normal	normal
3	muthukumar	65	m	2481	0	0	0	0	57	153	24.3	7.2			0.7	18	16	1.13	67	85	174						
4	ramesh	48	m	1009	0	0	1	0	70	172	23.7	7.3	4.5	2.8	1.4	41	39	1.05	131	100	140						
5	jayaraj	38	m	2428	0	0	0	0				6.8			1.2	33	29	1.14	200	125	198		1	e	n	normal	normal
6	rukumani	47	f	1044	0	1	0	0	60	148	27.4	7.1	4.3	2.8	0.6	21	18	1.17	74	100	180						
7	kalilrahman	55	m	2631	0	1	0	0				7.2			0.7	20	17	1.18	176	120			1	e	s	normal	n
8	kahil rahman	65	m	6542	0	1	0	0				7.2			0.7	20	17	1.18	176	140	210		1	n	n	normal	n
9	jaiburnisa	50	f	3451	0				60	153	25.6	7.7			0.8	23	19	1.21	158	120	250						
10	fathima	53	f	3903	0							6.7			0.9	36	27	1.33	195	160		208	n	n	n	n	n
11	sivaraj	45	m	1777	0							6.5			1	15	13	1.15	97			204	1	n	n	n	n
12	natarajan	47	m	2235	0	1	0	0	82	170	28.4	6.3			1.1	26	21	1.24	57	86	112		1	e	n	normal	normal
13	padma	42	f	861	0	0	1	0	60	153	25.6	6.9	4.3	2.6	0.7	15	12	1.25	91	90	140						
14	sisily	40	f	2528	0	1	0	0				6.8	4	2.8	0.8	21	19	1.11	136								
15	bagyam	63	f	7279	0	1	1	0	55	148	25.1	7.8	4.1	3.7	1.2	13	11	1.18	110	170	230		n	n	n	n	n
16	arumugham	55	m	2304	1	0	0	0	75	170	26.0	6.9	3.2		1	19	14	1.36	77				n	n	n	normal	normal
17	valliammal	60	f	2207	1	1	0	0												250	330						
18	vasantha	60	f	2251	1	1	0	0	53	145	25.2	6.2	4.1	2.1	1.5	35	32	1.09	127	110	180						
19	gangadaran	43	m	2548	1	1	1	0	45	160	17.6	7.1	4.1	3	1.5	35	32	1.09	125	120	210						
20	palanisamy	43	m	2548	1	0	1	0								26	21	1.25	112	113							
21	vishalakshi	65	f	2937	1	0	0	0								19	22	1.21	`109								
22	moideen	51	m	1246	1	1	0	0	60	167	21.5	7.9	4.5	3.4	0.9	24	15	1.60	108								
23	mohana	55	f	6545	1	1	1	0				7			0.9	19	14	1.36	104	180		197	1	n	n	n	n
24	tamilselvi	34	f	3861	1	1	1	0	62	154	26.1	7.1			0.9	19	15	1.27	78			261	1	n	n	n	n
25	baby	58	f	8515	1	1	0	0	80	150	35.6	7.3	4.3	3	0.8	41	38	1.08	104								
26	vasantham	30	f	1988	1	0	0	0	43	142	21.3	6.2	3.9	2.3	0.6	18	15	1.20	77	120	240						
27	palanisamy	50	m	5266	1	1	1	0	75	170	26.0	7.1	4.1	3	1.2	37	33	1.12	136	230	310						
28	soosai	55	m	965	1	1	0	0	55	153	23.5	7.3	4.2	3.1	0.8	17	15	1.13	80	80	150						
29	mariappan	62	m	930	1	1	0	0	64	165	23.5	6.8			0.8	18	15	1.20	131	160	290		n	n	n	normal	n
30	mahalakshmi	58	f	7412	1	1	0	0	55	152	23.8	7.2	3.9	3.2	0.7	18	15	1.20	103	170	270						
31	santhakumar	42	f	3215	1	1	0	0	65	158	26.0	7.2	3.9	3.3	0.6	19	14	1.36	113	130	230						
32	shaharvan	36	f	2666	1	1	0	0	60	153	25.6	6.9	3.7	3.2	0.6	18	15	1.20	108	190	250						
33	reetha mary	55	f	3214	1	1	1	0	72	155	30.0	7.7	4.2	3.5	0.6	16	10	1.60	72	100	160						
34	krishnaveni	60	f	2751	1	1	1	0	84	155	35.0	7			1.5	18	10	1.80	90	90	210	226					
35	saroja	61	f	1228	1	1	0	0	58	145	27.6	7.3			0.8	18	15	1.20	76			211	n	n	n	normal	n
36	shamuvel	30	f	1265	1	1	1	0				7.1	4.1	3	1	22	17	1.29	129	150	240						
37	duraisamy	50	m	2643	1	1	1	0	48	150	21.3	7.4			0.7	19	14	1.36	90	160		206	n	n	n	n	n
38	nagaraj	48	m	1779	1	1	1	0				6			0.5	19	17	1.12	104	190		210	1	n	n	n	n
39	senniyappan	61	m	2384	1	1	1	0				6.8			0.6	18	15	1.20	110			210	n	n	n	n	n
40	sivabakyam	53	f	2466	2	1	0	0	64	154	27.0	7.1			0.7	18	15	1.20	107				n	n	n	normal	normal
41	maruthachalam	60	m	2527	2	1	0	0	64	155	26.6	7.2	4.3	2.9	1.3	60	55	1.09	110	100	130						
42	sararthamani	45	f	772	2	1	1	0	52	150	23.1	6.8	4.8	2	1.2	27	25	1.08	163	90	120		n	n	n	normal	9mm
43	saraswathy	65	f	4521	2	1	1	0				7.2	4.3	2.9	0.6	21	17	1.24	166								
44	annairaj	47	m	4605	2	1	1	0				6.3			0.8	16	14	1.14	111			252	n	n	n	n	n
45	Backiam	60	f	1451	2	1	0	0	55	155	22.9	6.4	4.4	1.2	1.2	54	36	1.50	86				1	n	s		
46	vasantha	42	f	740	2	1	1	0																			
47	vasantha	51	f	1890	2	1	1	0	51	156	21.0	7.2	4.1	3.1	0.9	25	22	1.14	67	90	140						
48	rajammal	60	f	1635	2	1	1	0	77	164	28.6	6.5	2.4	2.4	1	35	32	1.09	174	200	230						
49	chacko	75	m	1143	2	1	0	0				7.3	4.2	3.1	0.9	35	30	1.17	121				n	n	n	distende	normal
50	amernuisa	70	f	3460	2	1	1	0															2	n	s	normal	normal
51	mohd yakoob	65	m	7463	2	1	0	0				7.5	4.6	2.9	0.7	25	21	1.19	90								
52	palanisamy	65	m	6517	2	1	0	0	54	155	22.5	7.4	4.5	2.9	1.5	23	19	1.21	122	90	180						
53	savitha	52	f	2537	2	1	1	0	63	153	26.9	6.8			0.7	17	19	0.89	74				1	n	n	normal	n
54	padmanaban	60	m	4581	2	1	0	0	75	160	29.3	6.4	3.7	2.7	0.6	14	12	1.17	116	100	190		n	n	n	normal	n
55	kalimuthu	54	m	451	2	1	0	0	67	163	25.2	6.6	4.3	2.3	1	17	15	1.13	124	113	260		1	n	n	normal	n
56	badurnisa	45	f	2232	2	1	0	0	75	156	30.8	7.2	4.7	3.1	0.4	15	12	1.25	182	110	190		1	n	n	6.6	n
57	kani	48	m	5181	2	1	0	0	80	164	29.7	7.6	4.5	3.1	0.7	20	18	1.11	162	140	250						
58	marulamani	60	m	8452	2	1	0	0	80	165	29.4	7.2	4.3	2.9	0.7	31	22	1.41	211	180	270						
59	pechiammal	57	f	5797	2	1	0	0	65	155	27.1	7.2	4	3.2	0.8	33	24	1.38	107								

Sl No	Name	Age	Sex	OP No	Duration	glibenclamide	Metformin	Insulin	Weight	Height	BMI	STP	S.ALB	S.GLOB	S.BIL	AST	ALT	AST/ALT	ALP	FBG	PPBG	T.CHOl	Fatty change	Size	Gall bladder	Bile ducts	Portal vein
60	rukumani	45	f	1542	2	1	1	0	64	155	26.6	7.2	4	3.1	1.2	46	35	1.31	103	110	170	154	n	n	n	n	n
61	sabiya	41	f	2757	2	0	1	0	84	156	34.5	7.2	4	3	0.6	23	17	1.35	177	105	165	223	1	n	n	normal	n
62	thankamma	62	f	5414	3	1	0	0	57	167	22.0	6.6	3.2	4	0.9	18	22	0.82	30	117	188	204	n	n	n	normal	
63	sakunthala	56	f	1511	3	1	1	0				6.9	3.9	3	0.6	21	17	1.24	80	154	243	175	n	n	n	n	n
64	arumugham	54	m	2467	3	1	1	0	77	170	26.6	7.1	4	3	1	21	25	0.84	112	132	221	128	n	n	n	normal	normal
65	kala	59	f	6617	3	1	1	0	67	155	27.9	6	4.1	1.9	0.5	18	12	1.50	67	140	180	163	n	n	n	5mm	10mm
66	gomathy	50	f	6751	3	1	1	0	58	155	24.1	6.8	3.9	2.9	0.9	15	13	1.15	67	100	180	155	n	n	n	7mm	n
67	chinnasamy	41	m	748	3	1	0	0	50	175	16.3	6.3	3.9	2.4	0.9	18	15	1.20	107	230	330	167					
68	chandrika	40	f	6650	3				57	155	23.7	7.6	4.2	3.4	0.8	17	11	1.55	161	110	240	154	n	n	n	normal	n
69	selvi	42	f	2352	3	1	0	1				7.3	4	3.3	0.9	21	19	1.11	180			178					
70	sundran	66	m	6910	3	1	0	0	60	165	22.0	7.3	4	3.3	0.9	19	16	1.19	95	140	270	145	n	n	s	6mm	n
71	kuthammal	60	f	8261	3	1	1	0	57	153	24.3	7.7	4.2	3.5	0.6	19	17	1.12	95	150	240	231					
72	arunachalam	44	m	3265	3	1	1	0	52	165	19.1	7.3	4	3	0.9	23	21	1.10	126	127	120	223	n	n	n	n	n
73	subramani	50	m	2963	3	1	0	0	54	164	####	7.4	4	3	1.1	20	15	1.33	174	132	165	328	n	n	n	n	n
74	sebastin	67	m	3688	4	1	0	0	59	171	19.8	7.6	5	3.2	0.9	20	17	1.18	63	87	121	147	n	e	n	5.5	11.8
75	mary	52	f	2605	4	1	1	0	65	168	20.6	6.4	3.2	2.9	0.9	26	42	0.62	120	190	240	137	1	n	s	normal	n
76	govindaraf	57	m	6523	4	1	0	0	90	175	29.4	7.1	4	3	0.8	21	15	1.40	93	70	122	142	1	n	n	normal	n
77	aysha beevi	45	f	3265	4	1	1	0	68	150	30.2	7.3	4.1	3.2	0.8	21	16	1.31	127	230	210	137					
78	jayakumar	60	m	989	5	1	0	0	67	155	27.9	6.6	4.5	2.5	1.6	21	15	1.40	59	154	211	199	n	n	n	normal	normal
79	venkatammal	58	f	6380	5	1	0	0	45	145	21.4	7.3	4.2	3.1	0.8	15	12	1.25	69	120	210	211	n	n	n	6.6mm	11mm
80	lakshman	58	m	2524	5	1	1	0	60	168	21.3	7.3	4	3	0.9	21	19	1.11	67		213	164				n	
81	kannmal	45	f	1542	5	1	1	0	67	156	22.0	6.5	4	2.5	1	32	28	1.08	121	123	187	138	n	n			
82	rajammal	56	f	1939	5	1	0	0	61	170	20.3	7.3	4.3	2.8	0.8	21	17	1.24	100	108	172	147			n	n	n
83	alagirisamy	56	m	2166	5				54	151	23.7	7.4	4.3	3.1	1.5	29	24	1.21	154	90	180	221	n		n		
84	marakadam	66	f	6758	5	1	0	0	62	148	28.3	6.4	4.2	2.2	1.1	22	18	1.22	131	110	180	207	n	n	n	normal	11mm
85	lakshmi	70	f	5784	5	1	0	0				7	4	3	0.8	19	16	1.19	121	132	203	179					
86	mariammal	50	f	6762	5	1	0	0								26	42	0.62	108	102	176	165					
87	lakshmi	55	f	4578	5	1	0	0				6.1	4	2	0.6	17	12	1.42	104	110	150	145	1	n	n	normal	n
88	rajendran	45	m	2712	5	1	0	0	58	162	22.1	7.1			0.8	19	14	1.36	155	140		286	n	n	n	normal	n
89	kamala	58	f	3919	5	1	1	0				7			1.1	20	18	1.11	107		178	218	1	n	n	n	n
90	krishnamurthy	60	m	1800	6	1	0	0	46	163	17.3	7.2	4.1	3	1.6	20	18	1.11	93	190	310	154	n	n	n	6mm	12mm
91	saroja	65	f	4613	7											18	15	1.20	124	132	231	194	n			n	
92	palanisamy	70	m	7823	8	1	1	0				6.3	4.1		2.1	47	34	1.38	118			188			n		n
93	kannama	60	f	3541	8	0	1	0	64	165	23.5	7.1	4.4		0.9	19	17	1.12	196	140	180	181		n		n	
94	selvamani	50	f	4553	8	1	1	0				7.3	4.3	3	0.7	28	25	1.12	189	140	235	168				n	n
95	jayalakshmi	55	f	4202	10	1	1	0				6.2	3.8	2.4	0.6	18	12	1.50	114			163		n			n
96	muthulakshmy	40	f	5931	10	1	0	0	60	157	24.3					19	1i9	1.00	98	102	176	191	1	n	n	normal	normal
97	sundarambal	63	f	8655	10							7	4			31	27	1.08	86	76	143	201	1	n	n	n	
98	lilly	65	f	6712	10	0	0	0	65	158	20.0	7.2	4	3.2	0.8	18	15	1.08	117	156	213	175	1	n	n	normal	normal
99	vijaya	36	f	1581	10	1	0	0	61	154	25.7	7.5	4.4	3.1	0.6	21	17	1.24	77	130	230	194	2	e	n	normal	norml
100	angathal	60	f	318	10	1	0	1								19	17	1.12	86	123		187		n			
101	paramaswaran	67	m	403	10	1	1	0	55	175	18.0	7.6	4.2	3.4	1.1	21	17	1.24	80	210	230	221				n	n
102	mariammal	45	f	7124	10	1	0	0	60	155	25.0	7.2	4.5	2.7	0.5	12	10	1.20	139	90	140	145	1	n	n	normal	n
103	banu	46	f	1551	10	1	0	0				6.9	4.5	2.4	1	16	14	1.14	99	140	190	174					n
104	hrudiya mary	67	f	6138	10	1	0	0	58	154	24.5	6.9	4.1	2.8	0.8	17	12	1.42	91			178					
105	devarajan	61	m	2949	10	1	1	0				7.5			1.5	30	28	1.07	57			235	n	n	n	n	n
106	saraswathy	67	f	1181	11	1	1	0				7.1	3.8		1.1	22	18	1.22	83			158				n	n
107	vembudurai	69	m	981	11	1	1	0	77	163	29.0	7.3	4.3	3	0.9	18	12	1.50	71			201		n			n
108	ramaraj	52	m	172	13	1	0	0	65	168	23.0	6.8	4.1	2.7	0.8	17	15	1.13	79	120	180	211				n	
109	sublakshmi	63	f	2390	15	0	0	0				6.9	3.7		0.6	19	17	1.12	103			196					
110	rajeshwari	53	f	2586	15	1	0	0	64	153	27.3	6.5			0.9	28	24	1.17	140			211	n	n	n	normal	n
111	thyagarajan	64	m	4302	15	1	0	0	74	173	24.7	7.4	4.2	3.2	1	22	18	1.22	153	90	250	154	n	n	n	normal	n
112	savithri	55	f	2345	15	1	1	0	55	155	22.9	7.1	4.2	2.9	0.5	19	17	1.12	128	120	140	173					
113	vijayarani	55	f	1635	17	1	0	0	75	163	28.2	7.1	3.9	3.2	1.1	27	18	1.50	114	220	240	176	n	n	n	n	n
114	kuppusamy	78	m	2545	20	0	2	0	52	165	19.1	7.6	4.7	2.9	0.8	24	21	1.14	169	130	240	201	n	n	n	n	n
115	latheef	70	m	760	22	1	1	0	49	165	18.0	6.8	4	2.8	0.8	19	16	1.19	67	90	110	185	n	n	n	n	n
116	pankakshi	75	f	7653	22	1	1	0	42	153	18.0	6.1	4	2	1	21	18	1.10	88	98	132	165	n	n	n	n	n
117	mehurnisa	56	f	2148	23	1	0	0	53	146	24.9	7.2	4	3.2	0.7	21	19	1.11	106	230	280	165					
118	rani	51	f	3985	26	1	1	0	48	148	21.0	7.1	4	3.1	0.8	24	20	1.20	105	180	125	227	1	n	n	n	n

PROFORMA

STUDY OF CLINICAL, BIOCHEMICAL,SONOLOGICAL PROFILE OF HEPATIC STATUS IN TYPE 2 DIABETES MELLITUS IN TERTIARY CARE SETTING

PROFORMA FOR DATA COLLECTION

CASE NO: _____ NAME: _____ HOSP NO:_____
AGE:_____

SEX:_____ DURATION OF DM2 :_____

SYMPTOMS

H/O PRESENT ILLNESS

H/O FATIGE

H/O ABDOMINAL DISCOMFORT

H/O GENERALISED SWELLING

PAST HISTORY

H/O DIABETES _____H/O HYPERTENSION_____

ON EXAMINATION

HEIGHT:_____-WEIGHT;_____BMI:_____

PERIPHERAL PULSES_____ BP_____-

SYSTEMIC EXAMINATION

ABDOMEN

LABORATORY EXAMINATION

BLOOD

LIVER FUNCTION TEST

SGOT: SGPT: ALP: T.BIL: TOTA PROT: ALB; GLOB:

LIPID PROFILE

CHOL: S. URIC ACID

BLOOD SUGAR

FASTING

POST PRANDIAL

ULTRASONOGRAM

LIVER SIZE

ECHOTEXTURE _____GRADE 1

GRADE 2

GRADE 3

BILIARY SYSTEM

PORAL VEIN

ABBREVIATIONS

NAFLD --- Non alcoholic fatty liver

NASH------Non alcoholic steato hepatitis

DM --------Diabetes mellitus

T CHOL----Total cholesterol

TG ----------Triglycerides

AST ---------Aspartate transaminase

ALT --------Alanine transaminase

ALP ----Alkaline phosphatase

STP ---------Serum total protein

HCC ---------Hepatocellular carcinoma

MS ----------Metabolic syndrome

HBV ---------Hepatitis B virus

HCV ---------Hepatitis C virus

BMI --------Body mass index

OHA --------Oral hypoglycemic agents